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Lipid and lipoprotein reference values from 133,450 Dutch Lifelines participants: Age- and gender-specific baseline lipid values and percentiles

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KEYWORDS:
Cholesterol;
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Reference values;
Cardiovascular risk factors;
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Familial hypercholesterolemia;
Lipid levels

BACKGROUND: Lipids and lipoproteins are recognized as the most important modifiable risk factors for cardiovascular disease. Although reference values for the major lipoproteins, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and triglycerides, have been collected in numerous studies and cohorts, complete contemporary percentile-based reference values are underreported.

OBJECTIVE: We set out to provide such reference lipid data using a large contemporary population-based cohort study.

STUDY DESIGN AND SETTING: Lifelines is a cross-sectional population-based Dutch cohort study. We analyzed 133,540 adult fasting participants without cardiovascular disease and without lipid-lowering drug use. Lipid levels were directly measured and selected percentiles of all lipid parameters were calculated. Friedewald LDL-C estimation was calculated as well.

RESULTS: From 20 till 49 years of age, men were found to exhibit a steep 64% increase of LDL-C (median +54 mg/dL), while triglyceride levels increased almost two-fold. In women, LDL-C levels did not change from 18 till 35 years, followed by a steep 42% increase till 59 years (median +42 mg/dL). In contrast to men, triglycerides were stable in ageing women. Overall, Friedewald LDL-C levels are lower compared with the direct measurement, especially with increasing triglyceride levels.

CONCLUSIONS: This observational study highlights striking gender- and age-related differences in plasma lipid profiles. The given reference ranges of plasma lipids can assist in early identification of individuals with hypocholesterolemia and hypercholesterolemia, especially familial hypercholesterolemia. These reference ranges are available for physicians and patients at www.my-cholesterol.care/.

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Introduction

Healthcare in the 21st century is challenged by an increasing number of people experiencing noncommunicable chronic diseases. Cardiovascular disease (CVD) affects most men beyond the age of 55 years and women beyond 65 years of age.[1] Consequently, CVD is generally regarded an ageing disorder. However, it has long been known that fatty streaks and subsequent plaque formation already starts at a very young age, and the pace of progression is related to plasma low-density lipoprotein cholesterol (LDL-C) levels concentration.[2] To curtail this threat, early prevention seems the preferred approach to curb this exponential increase in avoidable chronic diseases.[3,4] From this perspective, the early identification of modifiable risk factors, especially dyslipidemia, is key to effective prevention and management of CVD.[2,5]

Cohort studies can provide insight in what is needed to promote "healthy ageing" and find solutions for early identification and intervention of individuals at increased CVD risk. The Lifelines cohort study, initiated in 2006, is the largest ongoing prospective observational European population study to date.[6] Study participants, 152,180 adult inhabitants of the northern part of the Netherlands, were recruited by their primary care physicians, through family members or by registering at the Lifelines Website (www.lifelines.nl). The total duration of follow-up will be 30 years, the first 5-year follow-up visit is in process, the next 10-year follow-up visit is being planned. Data consist of self-reported/validated questionnaires, routine clinical biochemistry, physical examination, biobanking of biomaterials including blood, urine, and feces and genome-wide genotyping. Thereby, the Lifelines study can provide insight into the prevalence and incidence of multifactorial diseases and their risk factors, including lipids. Based on the concepts of modifiers and the three-generation design, this study may provide better understanding of the causes and prognosis of dyslipidemia over a lifetime. This may ultimately result in optimal tailored treatment of, for example, hypercholesterolemia, overriding standard preventive strategies.

Identifying dyslipidemia requires knowledge of the normal distribution of blood lipids in the population. Reference values for total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides have been collected in numerous studies and cohorts. However, contemporary and comprehensive percentile-based reference values are surprisingly missing. Apart from the broad variation of these values in different geographical regions,[7] there are also time-dependent changes reflecting modifications in age, lifestyle, and pharmaceutical interventions.[8,9]

This article aims to provide baseline information and facilitate future research, by providing age- and gender-based reference values for lipid levels. These lipid reference values are indispensable for comparison with populations from different regions or different genetic background, as well as monitoring prospective changes. Importantly, they can also serve the early identification of individuals with, for example, familial hypercholesterolemia, a common but underdiagnosed and undertreated genetic disease.[2]

Methods

Participants

Lifelines is a large population-based prospective cohort study conducted in the north of the Netherlands. Participants of almost exclusively Caucasian descent were included between 2006 and 2013. The study protocol was approved by the medical ethics committee of the University Medical Center Groningen, and all participants provided written informed consent. The design and rationale of the study are described elsewhere.[6] In short, general practitioners asked their patients, between the age of 25 and 50 years, if they were willing to participate. After a positive response, family members from all ages (partner, parents, parents-in-law, and children) were also invited to participate. In addition, individuals aged ≥18 years could become a participant through self-registration. These individuals were also asked to invite family members.

At baseline, all participants filled out questionnaires and underwent a comprehensive physical examination. The questionnaires covered health topics, psychosocial parameters, information on lifestyle, and medication use (including lipid-lowering drugs). Physical examination included anthropometry, blood pressure measurement, pulmonary function tests, echocardiogram, and a neuropsychiatric interview. Fasting blood was drawn from all participants for clinical chemistry measurements including plasma lipids.

Exclusion criteria

The data of children (aged <18 years) have not yet been released and could therefore not be included. Participants with a history of CVD at baseline, defined as myocardial infarction, coronary surgery (balloon angioplasty or bypass surgery) or stroke, were excluded. Transient ischemic attack and peripheral vascular disease could not be accounted for because these clinical features could not be adequately scored with the questionnaires used. In addition, participants reporting lipid-lowering drug use (ie, statins, fibrates, or ezetimibe) at baseline, and those with nonfasting blood tests at baseline were excluded from this analysis.

Cholesterol measurements

Venous blood samples were collected following a standard protocol, after an overnight fast. Plasma from heparinized tubes was used for clinical chemistry. Lipid measurements were performed using Roche Modular P automated analyzer (Mannheim, Germany). Total

cholesterol and LDL-C were measured with a direct enzymatic colorimetric assay using cholesterol esterase and cholesterol oxidase. Total cholesterol was standardized against isotope dilution-mass spectrometry and LDL-C was standardized against the beta quantification method. HDL-C was measured with a third-generation direct quantitative enzymatic colorimetric assay using polyethylene glycol-cholesterol esterase and polyethylene glycol-cholesterol oxidase and standardized against the CDC reference method.[10] Triglycerides were measured using an assay based on glycerol phosphate oxidase-peroxidase aminophenazone and standardized against isotope dilution-mass spectrometry. LDL-C was also calculated with the Friedewald formula (total cholesterol − HDL-C – [triglyceride/5.0]). When using this formula, 1387 individuals with triglyceride levels >400 mg/dL were excluded.[11] Apolipoprotein (Apo) B and ApoA-I were only measured in the first 6038 individuals that were enrolled. Because of the design of the Lifelines study, these 6038 individuals are between 25 and 50 years of age. Therefore, the data of Apo B and Apo A-I are not presented in this study.

Statistical analysis

All analyses were carried out using IBM SPSS Statistics, version 22.0 (IBM Corp, Armonk, NY). Baseline characteristics of normally distributed variables were reported as mean and standard deviation. Student's *t*-test was used to compare the means of two groups. Not normally distributed parameters were reported as median and interquartile range. Mann–Whitney U test was used to compare the medians between males and females.

Plasma lipid levels were analyzed for men and women separately at baseline. The 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles were calculated to display the population distribution. In addition, the 1st, 2.5th, 97.5th, and 99th percentiles were calculated. Kruskal–Wallis H test was used to determine differences in lipid levels between age groups within gender. Pairwise comparisons were performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. Adjusted *P* values are presented. To examine and describe trends of lipids with age, an adjusted *P* value ($P < .05$) was considered to be significant. To display the difference between calculated LDL-C and direct measurement of LDL-C, the median, 5th and 95th percentile of the absolute difference were plotted.

Results

Population characteristics

Of the 152,180 participants, 18,640 (12%) were excluded because of CVD, use of lipid-lowering drugs (statins, fibrates, or ezetimibe), nonfasting blood tests, or missing lipid data (Fig 1). Table 1 shows the baseline characteristics of the remaining 133,540 individuals, stratified by gender. The mean age of both men and women was 44 years (range 18–93 years). Our cohort consisted of more women (79,475; 60%) than men (54,065; 40%). Women presented with an overall more favorable cardiovascular risk profile than men: lower mean systolic blood pressure (122 vs 130 mm Hg; $P < .001$), lower median total cholesterol (193 vs 197 mg/dL; $P < .001$), lower median LDL-C (116 vs 131 mg/dL; $P < .001$), higher median HDL-C (62 vs 50 mg/dL; $P < .001$), lower triglycerides (77 vs 100 mg/dL; $P < .001$), and lower smoking rates (19.7 vs 23.3%; $P < .001$). An approximate quarter of the complete study population (23.6%) reported to be physically active for at least 30 minutes every day. Supplementary Table 1 shows the number of individuals included per gender and age group.

Figures 2 and 3 show the relation between age and blood lipid levels for men and women, using the 5th, 10th, 25th, 50th, 75th, 90th and 95th percentile lines. The text in the following sections only describes the main general observations. To illustrate the significance of some of these observations, we provide more detailed information for the 95th percentile or 5th percentile.

Age, gender, and LDL-C levels

At 20 years of age, men presented with significantly lower LDL-C levels compared with women (median: 85 vs 97 mg/dL; 95th percentile: 139 vs 151 mg/dL; $P < .001$). It is clear that in both genders LDL-C increases with age, but the dynamics were strongly gender specific: in men, LDL-C increased markedly from adolescence and peaked at 45 to 49 years of age (median: 139 mg/dL; 95th percentile: 197 mg/dL). At higher ages LDL-C levels show a gradual decrease. This is illustrated by men ≥ 80 years, whose LDL-C levels were significantly lower than those aged 60 to 64 years (median: 131 vs 143 mg/dL; 95th percentile: 183 vs 197 mg/dL; $P < .001$).

In women, by contrast, median LDL-C was stable until their mid-30s, after, which LDL-C increased to a maximum at 55 to 59 years (median: 143 mg/dL; 95th percentile: 205 mg/dL). There was no clear decline at higher ages in women as was observed in men. Another interesting finding is the enormous distribution of LDL-C levels in this apparently healthy general population. For example, in males, aged 35 to 39 years, 90% of the LDL-C levels are within 81 and 186 mg/dL.

While the current data were generated with direct lipid quantification methods, LDL-C is typically calculated using the Friedewald formula.[11] Calculated LDL-C in our study provides lower values compared with direct LDL-C quantification for both genders (Supplementary Fig. 1). The median Friedewald LDL-C was 7.0 mg/dL lower in men and 6.0 mg/dL lower in women. With increasing triglyceride levels, a greater absolute difference was noted.

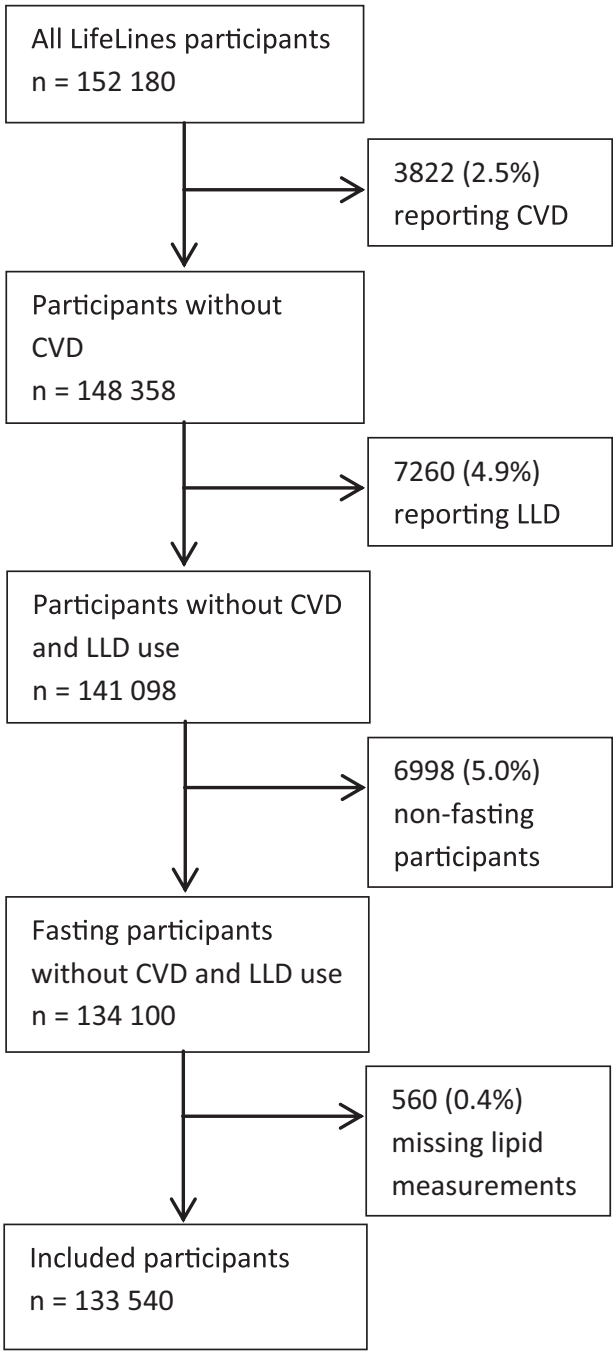

Figure 1 Outline of exclusion route. This figure shows how many and for which reasons participants were excluded. In total 18,640 individuals (12%) were excluded. CVD, cardiovascular disease; LLD, lipid-lowering drugs.

Age, gender, and HDL-C levels

In the different age groups of men, median HDL-C fluctuated between 46 and 54 mg/dL. In all age groups, apart from 35 to 39 years, the 5th percentile was 35 mg/dL. HDL-C did not significantly increase in older men. In women, median HDL-C increased from 54 mg/dL at young age (<20 years) to 66 mg/dL at the age of 50 years. Above the age of 50 years, no changes in HDL-C levels were noticed. The 5th percentile was 39 mg/dL in women aged <45 years and 43 mg/dL in those aged ≥ 45 years.

Age, gender, and triglyceride levels

Of all lipids, the relation between triglycerides and age showed the most pronounced differences between men and women. In men, triglyceride levels strongly increased from young age (median: 71 mg/dL; 95th percentile: 153 mg/dL) until 40 to 44 years of age (median: 106 mg/dL; 95th percentile: 289 mg/dL), thereafter, triglyceride levels dropped rapidly with advancing age. Interestingly, this increase was most prominent at the 75th, 90th, and 95th percentiles and almost absent at the 5th and 10th percentiles. In sharp contrast with the observations in men, triglyceride levels in women were relatively stable and median levels fluctuate between 68 and 77 mg/dL from 20 to 50 years of age. After 50 years of age, triglyceride levels increased moderately.

Reference values

Supplementary Tables 2 and 3 provide the (reference) values of all blood lipids (including total cholesterol and TC/HDL-C ratio) for men and women at five-year age intervals. These reference values are also available at www.my-cholesterol.care/. Supplementary Table 4 shows the effect of BMI on the age- and gender-specific 5th, 50th, and 95th percentiles.

Discussion

In this article, we describe the distribution of lipid and lipoprotein levels in the general adult population of the Netherlands. We anticipate that this large and unique cohort will provide the scientific and clinical community valuable new insights in the (near) future. Unique are the long and frequent follow-up visits; every 1.5 years participants fill in questionnaires, and every five years participants visit the Lifelines research site for a physical examination and biomaterial collection. Participants will be followed for at least 30 years. More than 6,000,000 samples of biomaterials will be stored in the Lifelines biobank. The innovative and unique three-generation design opens an exclusive opportunity for the study of the environmental as well as the genetic effects on lipid levels and CVD risk.

The presented lipid data from the Lifelines study provide several important findings:

(1) The analysis shows prominent gender- and age-related differences in all main plasma lipids and lipoproteins. Our analysis reveals the need to correct for age and gender when evaluating a lipid profile. Although these observations are cross-sectional, and conclusions on the true changes in lipids over time are hazardous, it is interesting to note that our cross-sectional data are comparable to the cross-sectional data from the Lipid Research Clinics (LRC) Prevalence study (see in the following).[12,13]

Table 1 Baseline characteristics of Lifelines cohort

Baseline characteristics	Total (n = 133,540)	Gender		*P* value
		Men (n = 54,065)	Women (n = 79,475)	
Age (y)	43.8 (12.6)	44.1 (12.6)	43.5 (12.6)	<.001
SBP (mm Hg)	125 (15)	130 (14)	122 (15)	<.001
DBP (mm Hg)	74 (9.3)	76 (9.4)	72 (8.8)	<.001
BMI (kg/m^2)	25.9 (4.3)	26.2 (3.6)	25.7 (4.7)	<.001
TC (mg/dL)	195 (170–220)	197 (174–224)	193 (166–220)	<.001
LDL-C (mg/dL)	124 (101–147)	131 (108–155)	116 (97–143)	<.001
HDL-C (mg/dL)	58 (46–66)	50 (43–58)	62 (50–73)	<.001
Triglycerides (mg/dL)	89 (62–120)	100 (72–144)	77 (58–105)	<.001
HbA1c (mmol/mol)	36 (34–39)	37 (34–39)	36 (34–39)	<.001
Smoking (%)	28,281 (21.2)	12,589 (23.3)	15,692 (19.7)	<.001
Physically active (%)	29,640 (23.6)*	11,815 (23.2)	17,825 (23.7)	.020
Diabetes mellitus (%)	1458 (1.1)	571 (1.1)	887 (1.1)	NS

DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, not significant; SBP, systolic blood pressure; TC, total cholesterol.

Baseline characteristics of complete cohort and separate for men and women. Normally distributed variables are presented as mean and standard deviation. Not normally distributed data are presented as median and interquartile range. Being physically active is defined as moderate physical activity of 30 min/d. SI conversion factors: to convert cholesterol parameters to mmol/L, multiply values by 0.02586. To convert triglycerides to mmol/L, multiply by 0.0113.

*A total of 7701 individuals did not answer this particular question.

(2) High LDL-C is common in the northern provinces of the Netherlands and the prevalence in young individuals is higher than anticipated. Many (young) individuals suffer from unknown hypercholesterolemia. Based on these outcomes, strategies to improve these modifiable risk factors need to be formulated at both the individual as well as population level.

(3) The data presented in this study, and the accompanying appendices, can be used as reference baseline values for the standard lipoprotein parameters: total cholesterol, LDL-C, HDL-C, and triglycerides. This will facilitate the evaluation of (population) interventions in the future and can be used as a comparator for other prospective or retrospective lipid profile analyses in different geographic regions. For use in clinical practice, an interactive Website is available at www.my-cholesterol.care/.

Reference values in clinical practice

We value early identification of individuals with increased LDL-C of utmost importance. Generating solid scientific evidence that early (lifestyle and, in high-risk individuals, pharmaceutical) intervention in primary care is beneficial, proves to be extremely difficult. Attempts to provide such evidence with one of the largest prospective cohort studies, the Copenhagen study group (personal communication with B.G. Nordestgaard) have failed because of lack of power. However, it is in our opinion a matter of common sense to reduce the burden of unhealthy lifestyle behaviors early in life, especially in individuals with LDL-C above the 95th percentile for age and gender. It was recently shown that counseling for a healthy lifestyle for five year led to lifelong (40 year) benefits.[14] Our data can be used to show individuals why they must act to attenuate the potential increase of their high LDL-C levels.

Using the cut-off levels of the 1st and 99th percentiles, extreme lipid phenotypes can be identified, facilitating early identification of hypercholesterolemia and hypocholesterolemia in patients (and their families at increased CVD risk). Further examination of these individuals would allow for in-depth analysis of the underlying causes of these severe dyslipidemias, generating opportunities to unravel (novel) pathways that are related to hypocholesterolemia and hypercholesterolemia. Apart from LDL-C, our data could also be of use in the identification of individuals with extremely low HDL-C, which is a useful marker for poor prognosis.[15]

Our study shows an impressive increase in LDL-C with ageing. When using fixed LDL-C cut-off values, young individuals with age- and gender-corrected very high LDL-C are in peril of not being identified as having an increased CVD risk. Why appropriate identification of these young individuals is so important was shown in the Atherosclerosis Risk in Communities study.[16] Afro-American individuals with a proprotein convertase subtilisin/kexin type 9 (*PCSK9*) loss of function mutation presented with a 28% reduction in LDL-C, this translated into an impressive 88% reduction of CVD risk. Caucasian carriers of another *PCSK9* loss of function mutation presented with a reduction of only 15% in LDL-C levels, but a striking 47% reduction in CVD risk. An explanation for these remarkable observations is that individuals with a loss of function mutations in PCSK9 benefit from lifelong lower LDL-C levels.

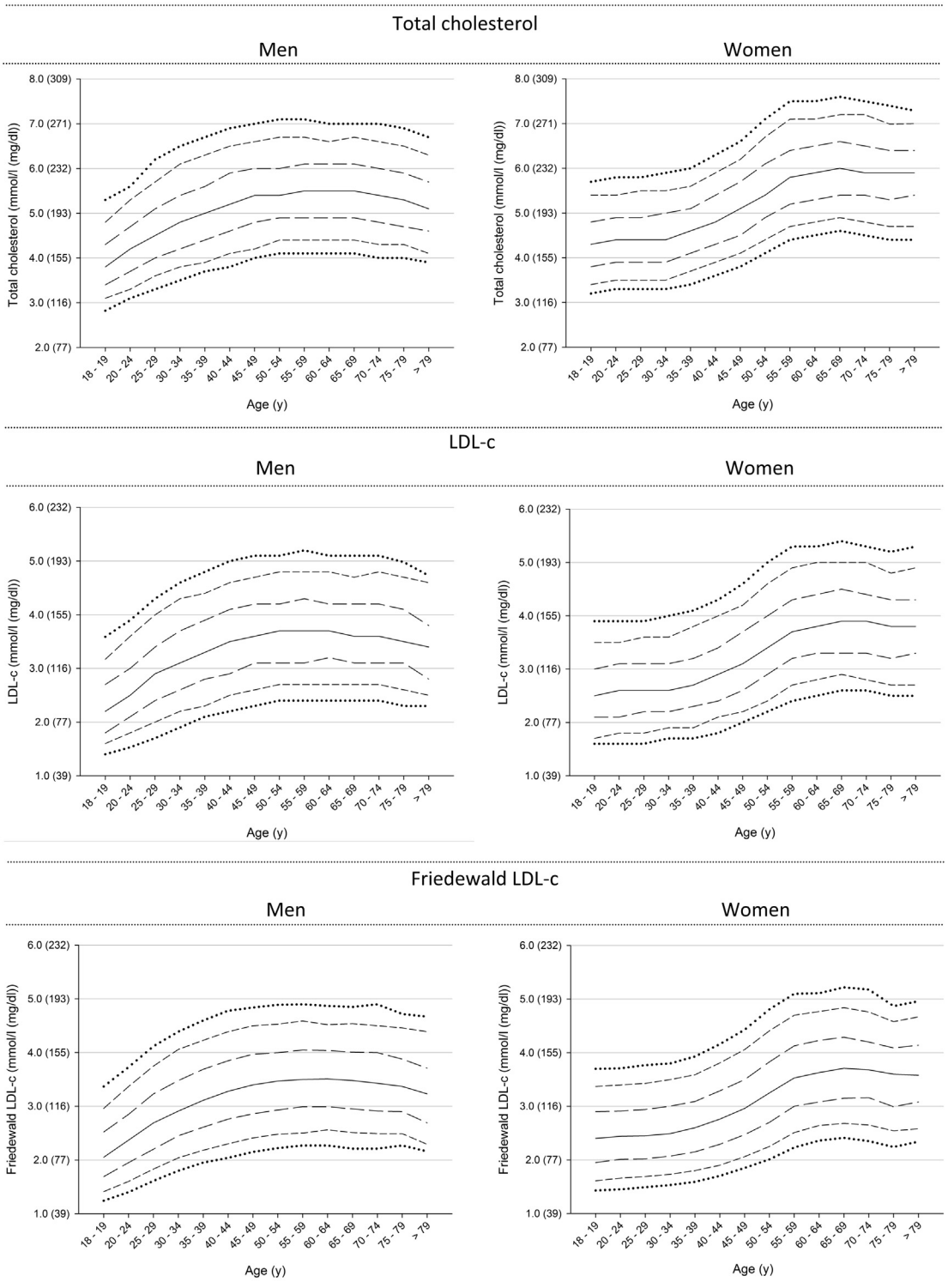

Figure 2 Relations between age and levels of total cholesterol, LDL-C, and calculated LDL-C in men and women. The 5th, 10th, 25th, 50th, 75th, 90th and 95th age-specific percentile curves for total cholesterol, LDL-C, and calculated LDL-C (using Friedewald formula) in men (left) and women (right). LDL-C, low-density lipoprotein cholesterol.

Comparing the Lifelines to other cohort studies

To our knowledge, currently used lipid reference values are largely based on the cross-sectional LRC Prevalence study that was carried out in the 1970s.[12,13] Figure 4 shows the comparison of total cholesterol, LDL-C, and triglycerides of these studies. In men, only very small differences in total cholesterol between the studies were observed. Women in Lifelines, however, presented with approximately 6.0 mg/dL lower total cholesterol levels between

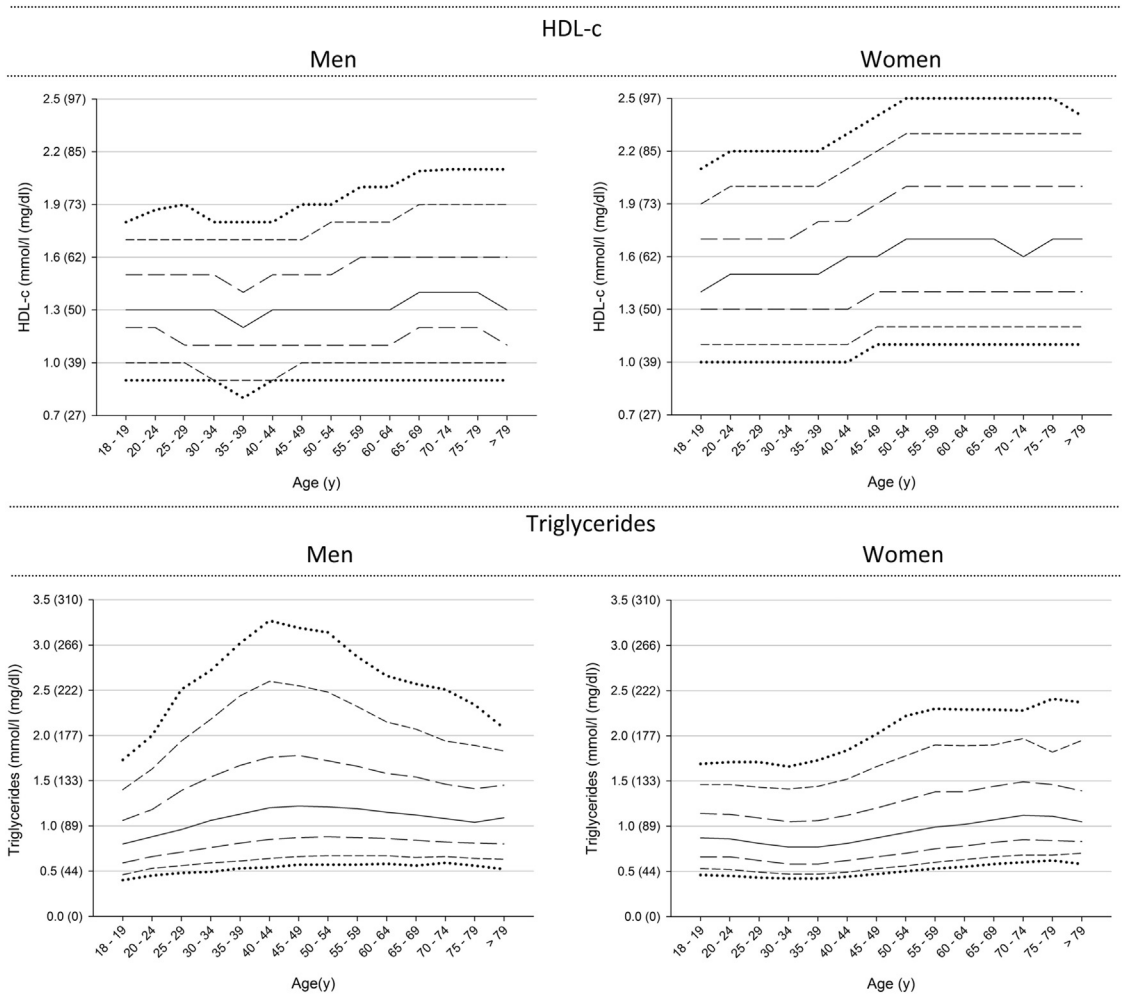

Figure 3 Relations between age and levels of HDL-C and triglycerides in men and women. The 5th, 10th, 25th, 50th, 75th, 90th and 95th age-specific percentile curves for HDL-C and triglycerides in men (left) and women (right). HDL-C, high-density lipoprotein cholesterol.

the ages of 30 to 55 years. A similar pattern is also present in distribution of LDL-C. Triglycerides seem to be lower in the Lifelines study in all percentiles, however, the patterns are comparable.

The similarity of the LDL-C distribution among both studies is surprising in the context of the National Health and Nutrition Examination Surveys (NHANES) showing nation-wide improvements in lipid levels in the United States over the past 60 years.[17–19] This phenomenon may also apply for the situation in the north of the Netherlands. We can speculate that total cholesterol levels may have been higher in our study population in the 1970s. Alternatively, the Lifelines population may currently still reflect the situation of the 1970s in the United States. We have recently shown that the overall adherence to guidelines is quite poor,[20] and this could also apply to improved lifestyle changes. In this regard, still 21% of the population smokes tobacco. Another point that may merit attention is that we have excluded individuals reporting lipid-lowering medication. The use of lipid-lowering drugs become more widely accepted after the Prevalence study, and lipid-lowering drug use certainly have a huge effect on total cholesterol distribution curves. Difference in the cholesterol analysis methods might also explain the higher total cholesterol levels observed in Lifelines. However, only in middle-aged females, total cholesterol levels were lower. As this effect is gender specific, it is unlikely to be related to differences in methods of measurements only. This is not in-line with an overall technical issue underlying our observations. It should also be noted that not all population studies show a decrease in cholesterol levels over time in all age groups. For example, the Minnesota Heart Survey showed that between 1980 and 2002, no changes in lipid levels were present in individuals aged between 25 and 44 years.[21] It is likely that this also applies to the Lifelines population.

A direct comparison of mean calculated LDL-C levels between NHANES[22] and Lifelines population shows that calculated LDL-C levels are similar across all age groups, apart from 30 to 39 years, where LDL-C appears lower in the Lifelines cohort (see Supplementary Table 5). LDL-C means of the complete Lifelines cohort (including

individuals reporting CVD and lipid-lowering drugs) are more comparable to the NHANES study in comparison to Lifelines individuals without CVD and lipid-lowering drug use. The mean LDL-C levels from Question diagnostics[23] are substantially lower across all age groups (see Supplementary Table 5). This is probably due to methodology: the latter population is a patient-based sample.

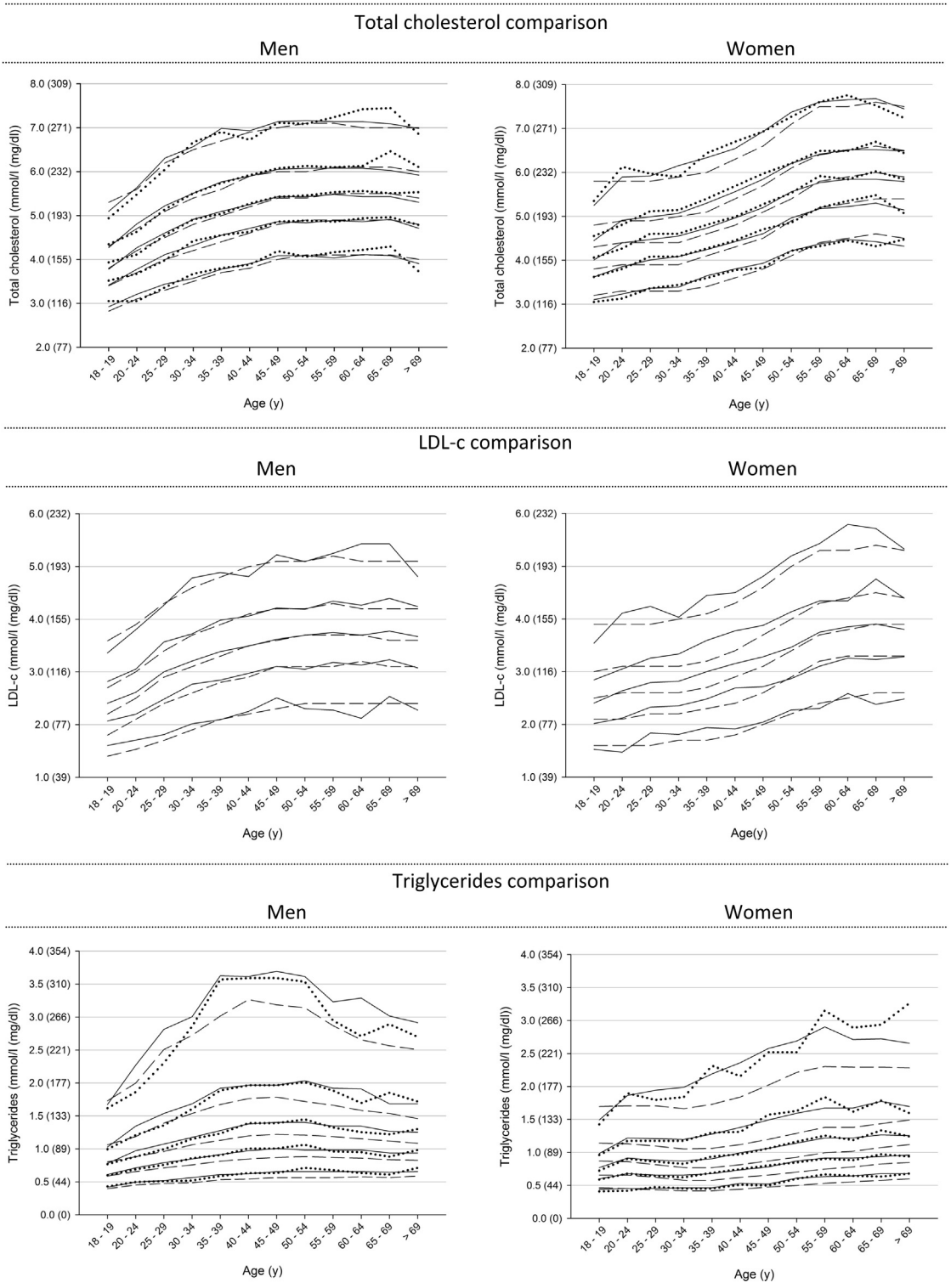

Figure 4 Comparing levels of total cholesterol, LDL-C, and triglycerides as measured in the LRC Prevalence study, the AHA special report, and the Lifelines study. The 5th, 25th, 50th, 75th, and 95th age-specific percentile curves for total cholesterol, LDL-C, and triglycerides are presented for the LRC Prevalence study (solid line),[12] the AHA special report (dotted line),[13] and Lifelines study (interrupted line), in men and women. LDL-C levels from Prevalence study and AHA special report were similar. LDL-C, low-density lipoprotein cholesterol; LRC, Lipid Research Clinics; AHA, American Heart Association.

Direct vs calculated measurement of LDL-C

In the Lifelines study, the median Friedewald LDL-C was overall 7.0 mg/dL lower in men, and 6.0 mg/dL in women, compared with direct LDL-C measurements. Many studies have investigated the difference between direct measurement and calculated LDL-C. It was shown in 27,331 healthy women that direct measurement was also lower compared with the Friedewald equation. However, both methods showed similar association of LDL-C with CVD.[24] In a large American study, it was also shown that Friedewald-estimated LDL-C levels were lower than the direct measurement, especially at low LDL-C levels (<70 mg/dL) and high triglyceride levels.[25] For an extensive and fair comparison, the measurements should be compared with ultracentrifugation, the golden standard. This process is however not suited for large-scale routine use and therefore not available in our cohort. In clinical practice, however, both the direct measurement as the calculated LDL-C are often used. This analysis reemphasizes the need to answer the question whether the Friedewald or direct measurement should be used in treatment decisions.

Strengths and weaknesses

The large sample size of participants and the comprehensive data that are collected makes this a unique cohort primed for translational research analysis. In Lifelines, approximately one-third of the participants' family members participated, providing a unique opportunity to analyze genetic traits. The Lifelines cohort is a large representative sample of the general population of the north of the Netherlands.[26] Because of multiple recruitment strategies including general practitioners' patient files, family referral, and self-registration, a representative study sample was achieved. Lifelines is broadly representative on lifestyle, diseases, and general health. The risk of selection bias is low. However, middle-aged men and women are overrepresented. Because we investigated the effect of age on gender on lipid parameters, this could not have influenced our results.

A limitation is that the data set used is cross-sectional but so far, references values were based on the likewise cross-sectional (very similar) data of the LRC Prevalence study. Naturally, prospective data will become available (earliest autumn 2017). Generalizability of this study is limited because participating was and is voluntary, so that the study sample was self-selected. Another unfortunate limitation is that the participants of Lifelines are almost exclusively of Caucasian descent. Thus, our reference ranges will not be applicable to other ethnicities: more than 98% of the Lifelines cohort is of Caucasian Northern/West European descent.

Conclusions

Our data show prominent differences in lipid profiles between gender and age. This study provides tools, that is, gender- and age-specific reference values of contemporary blood lipid levels (available at www.my-cholesterol.care/) that may be used to identify young individuals with atherogenic dyslipidemia, and therefore increased risk of CVD.

Acknowledgements

J.W.B. and I.M.N. had full access to all the data in the study and take responsibility for the integrity of data and the accuracy of the data analysis.

Disclosure

The authors declare that they have no conflicts of interest.

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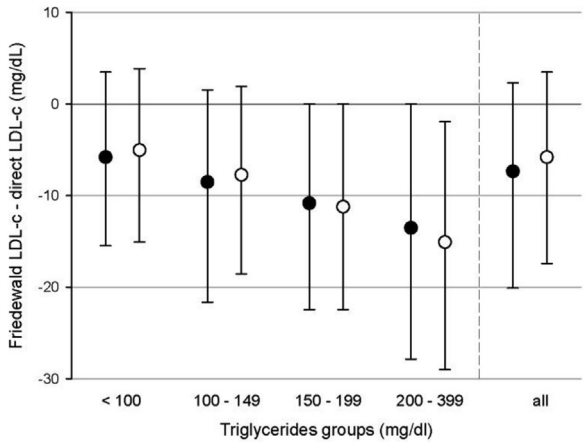
Appendix



Supplementary Figure 1 Absolute difference in calculated Friedewald LDL-C and direct LDL-C measurement by triglyceride strata. The absolute difference between Friedewald LDL-C and direct measurement of LDL-C by triglyceride strata are presented as median (circles) and the 5th and 95th percentile (error bars), separately for men (black) and women (white). Values below zero indicate that the direct measurement is higher than the Friedewald calculation and vice versa. To convert cholesterol parameters to mmol/L, multiply values by 0.02586. To convert triglycerides to mmol/L, multiply by 0.0113.

Supplementary Table 1 Number of participants stratified by 5-year age groups

	Gender		
	Men	Women	Total
Age group	Baseline	Baseline	Baseline
18–19	842	1616	2458
20–24	1905	3995	5900
25–29	4638	6576	11,214
30–34	5302	7059	12,361
35–39	6485	9535	16,020
40–44	8822	13,129	21,951
45–49	10,049	14,789	24,838
50–54	5705	8289	13,994
55–59	3338	5166	8504
60–64	3227	4502	7729
65–69	2182	2794	4976
70–74	1013	1284	2297
75–79	383	520	903
≥80	174	221	395
Total	54,065	79,475	133,540

Supplementary Table 2 Age-specific percentile values for total cholesterol, LDL-C, HDL-C, TC/HDL-C ratio, and triglycerides in men

Percentile	1st	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
TC (mg/dL)											
18–19 y	97	104	109	120	131	147	166	186	205	220	234
20–24 y	101	112	120	128	143	162	182	205	217	232	243
25–29 y	108	120	128	139	155	174	197	220	240	255	273
30–34 y	116	128	135	147	162	186	209	236	251	267	286
35–39 y	124	131	143	151	170	193	217	244	259	275	294
40–44 y	128	139	147	159	178	201	228	251	267	282	302
45–49 y	131	143	155	162	186	209	232	255	271	286	302
50–54 y	135	147	159	170	189	209	232	259	275	286	305
55–59 y	139	151	159	170	189	213	236	259	275	286	302
60–64 y	135	147	159	170	189	213	236	255	271	286	302
65–69 y	135	147	159	170	189	213	236	259	271	282	298
70–74 y	128	143	155	166	186	209	232	255	271	282	302
75–79 y	128	143	155	166	182	205	228	251	267	280	295
≥80 y	139	145	151	159	178	197	220	244	259	267	296
LDL-C (mg/dL) direct measurement/calculated (Friedewald formula)											
18–19 y	43/39	50/42	54/47	62/54	70/65	85/79	104/97	123/114	139/130	147/141	162/155
20–24 y	46/40	54/48	59/54	70/62	81/75	97/91	116/110	139/130	151/144	164/157	182/171
25–29 y	50/45	62/56	66/62	77/70	93/85	112/104	131/124	155/145	166/159	182/171	197/190
30–34 y	58/52	70/62	73/69	85/79	101/94	120/112	143/134	166/157	178/169	193/184	213/200
35–39 y	62/58	73/67	81/75	89/84	108/100	128/120	151/142	170/163	186/178	201/190	217/209
40–44 y	66/61	77/70	85/79	97/89	112/106	135/126	159/148	178/169	193/185	205/195	220/212
45–49 y	70/63	81/74	89/83	101/93	120/110	139/131	162/153	182/174	197/187	209/198	224/212
50–54 y	70/66	81/76	93/86	104/96	120/113	143/134	162/154	186/175	197/189	213/202	228/217
55–59 y	75/71	85/80	93/87	104/96	120/115	143/135	166/156	186/177	201/189	213/201	228/216
60–64 y	73/67	85/79	93/87	104/99	124/115	143/135	162/156	186/174	197/188	209/199	227/215
65–69 y	73/65	81/75	93/85	104/97	120/114	139/134	162/155	182/175	197/187	205/199	220/212
70–74 y	58/58	81/78	93/85	104/96	120/112	139/132	162/155	186/174	197/189	209/198	224/215
75–79 y	69/65	81/78	89/87	101/96	120/112	135/130	159/149	182/172	193/182	206/195	217/205
≥80 y	73/67	80/75	89/83	97/88	108/104	131/125	147/143	178/169	183/180	196/197	213/209
HDL-C (mg/dL)											
18–19 y	31	35	35	39	46	50	58	66	73	77	81
20–24 y	31	31	35	39	46	50	58	66	72	77	85
25–29 y	27	31	35	39	43	50	58	66	73	77	81
30–34 y	27	31	35	35	43	50	58	66	70	73	85
35–39 y	27	31	31	35	43	46	54	66	70	77	81
40–44 y	27	31	35	35	43	50	58	66	70	77	81
45–49 y	27	31	35	39	43	50	58	66	73	81	85
50–54 y	31	31	35	39	43	50	58	70	73	81	89
55–59 y	31	31	35	39	43	50	62	70	77	85	89
60–64 y	31	31	35	39	43	50	62	70	77	85	92
65–69 y	31	35	35	39	46	54	62	73	81	85	93
70–4 y	31	35	35	39	46	54	62	73	81	85	93
75–79 y	31	35	35	39	46	54	62	73	81	89	97
≥80 y	27	32	35	39	43	50	62	73	81	89	97
TC/HDL-C ratio											
18–19 y	1.75	1.88	1.95	2.15	2.46	2.83	3.37	3.93	4.42	4.82	5.33
20–24 y	1.81	1.95	2.10	2.25	2.63	3.09	3.79	4.55	5.14	5.64	6.46
25–29 y	1.90	2.10	2.25	2.46	2.86	3.47	4.25	5.11	5.80	6.40	7.21
30–34 y	2.00	2.19	2.38	2.63	3.11	3.78	4.60	5.50	6.11	6.78	7.75
35–39 y	2.12	2.30	2.53	2.79	3.31	4.00	4.91	5.91	6.56	7.30	8.25
40–44 y	2.11	2.36	2.56	2.85	3.40	4.15	5.09	6.00	6.70	7.40	8.33
45–49 y	2.11	2.35	2.56	2.85	3.44	4.18	5.08	6.00	6.60	7.14	7.89
50–54 y	2.14	2.39	2.60	2.92	3.44	4.17	5.00	5.89	6.50	7.13	8.00
55–59 y	2.14	2.35	2.59	2.85	3.38	4.13	5.00	5.83	6.43	7.00	7.83
60–64 y	2.18	2.41	2.60	2.88	3.40	4.07	4.85	5.67	6.20	6.77	7.44

(*continued on next page*)

Supplementary Table 2 (*continued*)

Percentile	1st	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
65–69 y	2.11	2.35	2.56	2.85	3.31	3.93	4.73	5.55	6.09	6.60	7.13
70–74 y	2.08	2.40	2.58	2.81	3.29	3.92	4.72	5.42	5.94	6.41	7.20
75–79 y	2.09	2.30	2.48	2.72	3.23	3.83	4.62	5.50	5.91	6.40	6.92
≥80 y	2.14	2.24	2.30	2.62	3.25	3.85	4.61	5.50	5.77	6.57	7.64
Triglycerides (mg/dL)											
18–19 y	27	32	35	41	52	71	94	124	153	187	221
20–24 y	31	35	40	47	58	78	105	144	177	220	291
25–29 y	32	37	42	50	63	85	123	172	222	280	376
30–34 y	35	39	43	52	67	94	136	193	241	304	398
35–39 y	35	42	47	54	72	100	148	216	267	335	468
40–44 y	37	42	48	57	75	106	156	230	289	367	517
45–49 y	39	44	50	58	77	108	158	226	282	350	436
50–54 y	38	44	50	59	78	107	152	220	278	359	488
55–59 y	39	44	50	59	77	105	147	205	254	322	439
60–64 y	41	45	51	59	76	102	140	190	235	286	365
65–69 y	40	44	50	58	74	99	136	183	227	276	334
70–74 y	42	46	52	58	73	96	129	172	222	266	344
75–79 y	38	45	50	57	72	92	125	167	207	261	301
≥80 y	37	42	46	56	71	97	128	162	184	207	337

TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC/HDL-C ratio, total cholesterol/HDL-C ratio.

SI conversion factors: to convert cholesterol parameters to mmol/L, multiply values by 0.02586. To convert triglycerides to mmol/L, multiply by 0.0113.

Supplementary Table 3 Age-specific percentile values for total cholesterol, LDL-C, HDL-C, TC/HDL-C ratio, and triglycerides in women

Percentile	1st	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
TC (mg/dL)											
18–19 y	108	116	124	131	147	166	186	209	220	232	247
20–24 y	112	120	128	135	151	170	189	209	224	236	251
25–29 y	112	120	128	135	151	170	189	213	224	240	259
30–34 y	112	124	128	135	151	170	193	213	228	240	255
35–39 y	116	124	131	143	159	178	197	217	232	244	263
40–44 y	124	131	139	151	166	186	209	228	244	255	275
45–49 y	131	139	147	159	174	197	220	240	255	271	290
50–54 y	139	151	159	170	189	209	236	259	275	290	313
55–59 y	147	159	170	182	201	224	247	275	290	302	321
60–64 y	155	165	174	186	205	228	251	275	290	305	325
65–69 y	151	166	178	189	209	232	255	278	294	305	329
70–74 y	151	162	174	186	209	228	251	278	290	302	322
75–79 y	147	162	170	182	205	228	247	270	286	298	309
≥80 y	153	166	170	182	209	228	247	271	282	294	314
LDL-C (mg/dL) direct measurement/calculated (Friedewald formula)											
18–19 y	47/42	54/49	62/55	66/62	81/75	97/93	116/112	135/130	151/143	159/154	182/172
20–24 y	46/42	54/49	62/56	70/64	81/78	101/94	120/112	135/131	151/143	159/155	178/169
25–29 y	46/42	54/50	62/57	70/65	85/78	101/95	120/113	139/132	151/145	166/159	182/176
30–34 y	50/43	58/52	66/59	73/67	85/80	101/96	120/116	139/135	155/147	166/160	182/177
35–39 y	50/46	58/54	66/61	73/69	89/83	104/100	124/119	147/138	159/152	170/163	189/181
40–44 y	54/48	62/58	70/65	81/73	93/88	112/106	131/127	155/147	166/160	182/173	197/191
45–49 y	62/53	70/63	77/71	85/80	101/95	120/114	143/135	162/157	178/171	193/186	209/202
50–54 y	66/59	77/70	85/78	93/87	112/104	131/125	155/148	178/170	193/186	209/199	232/221
55–59 y	73/66	81/77	93/86	104/97	124/116	143/137	166/159	189/182	205/197	220/209	236/226
60–64 y	77/73	89/83	97/91	108/102	128/119	147/140	170/163	193/184	205/197	220/210	240/229
65–69 y	77/73	93/85	101/93	112/103	128/121	151/143	174/165	193/187	209/201	224/215	244/235
70–74 y	77/71	89/81	101/90	108/102	128/122	151/142	170/162	193/184	205/200	217/210	240/228
75–79 y	73/62	85/75	97/87	104/97	124/115	147/139	166/158	186/177	201/188	209/200	228/214
≥80 y	81/71	87/77	97/90	104/99	128/119	147/138	166/160	189/180	205/191	220/211	236/228
HDL-C (mg/dL)											
18–19 y	35	35	39	43	50	54	66	73	81	85	93
20–24 y	35	35	39	43	50	58	66	77	85	89	97
25–29 y	35	35	39	43	50	58	66	77	85	93	97
30–34 y	31	35	39	43	50	58	66	77	85	89	97
35–39 y	35	39	39	43	50	58	70	77	85	89	97
40–44 y	35	39	39	43	50	62	70	81	89	93	101
45–49 y	35	39	43	46	54	62	73	85	93	97	108
50–54 y	35	39	43	46	54	66	77	89	97	104	112
55–59 y	35	39	43	46	54	66	77	89	97	104	116
60–64 y	39	39	43	46	54	66	77	89	97	104	116
65–69 y	35	39	43	46	54	66	77	89	97	104	112
70–74 y	35	39	43	46	54	62	77	89	97	104	112
75–79 y	32	39	43	46	54	66	77	89	97	104	111
≥80 y	35	39	43	46	54	66	77	89	93	97	108
TC/HDL-C ratio											
18–19 y	1.76	1.90	2.00	2.17	2.50	2.93	3.50	4.17	4.67	5.17	5.73
20–24 y	1.74	1.86	2.00	2.13	2.47	2.93	3.50	4.09	4.50	4.92	5.62
25–29 y	1.74	1.86	2.00	2.14	2.45	2.88	3.47	4.17	4.69	5.20	5.83
30–34 y	1.73	1.89	2.00	2.17	2.47	2.93	3.54	4.23	4.78	5.33	6.10
35–39 y	1.75	1.89	2.00	2.17	2.47	2.93	3.54	4.25	4.82	5.33	6.09
40–44 y	1.75	1.89	2.05	2.19	2.53	3.00	3.68	4.42	5.00	5.55	6.33
45–49 y	1.76	1.94	2.06	2.25	2.60	3.10	3.77	4.58	5.18	5.73	6.50
50–54 y	1.83	2.00	2.13	2.30	2.67	3.21	3.93	4.79	5.39	6.00	6.67
55–59 y	1.87	2.03	2.21	2.41	2.80	3.40	4.14	5.00	5.50	6.06	6.70
60–64 y	1.92	2.11	2.26	2.48	2.88	3.44	4.21	5.00	5.58	6.08	6.82

(*continued on next page*)

Supplementary Table 3 (*continued*)

Percentile	1st	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
65–69 y	2.00	2.17	2.33	2.52	2.95	3.50	4.22	5.00	5.57	6.09	6.64
70–74 y	1.97	2.19	2.34	2.50	3.00	3.56	4.27	5.00	5.46	5.92	6.83
75–79 y	1.82	2.10	2.25	2.52	2.86	3.42	4.13	4.92	5.60	6.43	6.97
≥80 y	2.06	2.22	2.36	2.50	2.85	3.33	4.12	4.92	5.75	6.11	6.55
Triglycerides (mg/dL)											
18–19y	32	36	41	47	58	77	101	129	150	174	199
20–24 y	30	35	40	46	58	76	100	129	151	172	202
25–29 y	30	34	38	43	55	72	97	127	151	180	217
30–34 y	29	33	37	42	51	68	93	125	147	177	216
35–39 y	30	34	37	42	51	68	94	127	153	181	235
40–44 y	31	35	39	43	55	72	99	135	163	196	245
45–49 y	34	38	42	47	58	77	106	147	179	214	274
50–54 y	35	40	44	50	62	82	114	158	196	237	290
55–59 y	37	42	47	53	66	88	122	168	204	244	291
60–64 y	39	44	49	56	69	90	122	167	203	242	306
65–69 y	42	47	51	58	73	95	127	168	203	237	290
70–74 y	42	48	53	60	75	99	132	174	202	226	276
75–79 y	39	50	55	60	74	98	129	161	213	259	292
≥80 y	40	47	51	62	73	93	123	172	210	235	253

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC/HDL-C ratio, total cholesterol/HDL-C ratio; TC, total cholesterol.

SI conversion factors: to convert cholesterol parameters to mmol/L, multiply values by 0.02586. To convert triglycerides to mmol/L, multiply by 0.0113.

Supplementary Table 4 The fifth, median, and 95th percentile of LDL-C are presented for age and gender groups, but also for specific BMI groups

LDL-C (mg/dL) males					LDL-C (mg/dL) females				
	BMI (kg/m^2)					BMI (kg/m^2)			
Age (y)	<25	25–30	30–35	≥35	Age (y)	<25	25–30	30–35	≥35
18–19	54–85–128	60–101–152	N/A*	N/A	18–19	58–97–143	61–104–159	66–112–170	N/A
20–24	58–93–143	66–108–62	58–116–182	N/A	20–24	58–97–143	66–104–155	70–108–162	69–104–155
25–29	66–104–159	70–116–174	80–124–178	90–124–176	25–29	62–97–147	66–104–159	73–112–162	70–112–173
30–34	73–112–174	81–124–182	85–131–193	63–120–182	30–34	62–97–147	66–104–159	72–112–166	68–116–166
35–39	77–120–178	85–131–189	89–135–189	76–131–189	35–39	66–101–147	70–112–162	73–116–170	70–116–174
40–44	81–128–186	89–139–197	89–139–201	93–135–189	40–44	70–108–159	73–116–174	77–124–178	77–120–174
45–49	85–131–193	93–143–197	93–143–197	85–135–195	45–49	73–116–170	81–124–182	81–128–189	85–128–183
50–54	89–139–197	97–143–201	89–143–201	73–139–195	50–54	81–128–189	85–135–197	89–135–193	89–139–205
55–59	93–139–193	93–143–201	95–147–205	93–143–220	55–59	90–139–198	93–147–213	89–147–213	83–139–201
60–64	93–139–193	97–143–198	93–143–197	88–128–197	60–64	97–147–205	101–151–209	97–151–205	101–143–193
65–69	89–139–193	97–143–197	89–143–189	N/A	65–69	97–147–209	104–155–209	97–151–213	93–147–201
70–74	89–135–193	97–143–199	85–139–189	N/A	70–74	102–151–209	101–151–205	93–143–209	N/A
75–79	97–131–182	87–139–197	N/A	N/A	75–79	97–151–205	93–143–197	104–51–197	N/A
≥80	78–124–182	93–133–188	N/A	N/A	≥80	95–143–205	97–153–207	N/A	N/A

BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; N/A, not applicable.

*N/A: <60 individuals were present in these subgroups.

Supplementary Table 5 Mean Friedewald LDL-C of NHANES 2003 to 2004 study in comparison to Question diagnostics population 2008 to 2011 and the Lifelines population

Age (y)	NHANES 2003–2004 (mg/dL)[1]	Quest diagnostics population 2008–2011 (mg/dL)[2]	Lifelines I (mg/dL)	Lifelines II (mg/dL)
20–29	104	95	99	99
30–39	120	107	110	108
40–49	124	111	120	119
50–59	123	111	133	130
60–69	126	104	140	130
70–79	119	97	138	123

LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Surveys.

Lifelines I: fasting Lifelines participants without cardiovascular disease and without statin use and triglyceride 400 mg/dL. Similar population as in our study. Lifelines II: fasting Lifelines participants.

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